IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Schwarz

U.S. Patent App'n Ser. No.: 10/589,924 Group: 1615

Filed: 18 August 2006 Examiner: Ahmed, Hasan Syed

Atty. Docket No.: 33660-US-PCT

Title: AMOXICILLINE INSTANT GRANULATE

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the rejection of claims 36-58 of the subject application.

(i). Real Party in Interest:

This application is owned by Sandoz AG.

(ii). Related Appeals and Interferences:

There are **no** other prior or pending appeals, interferences or judicial proceedings known to Appellant, the Appellant's legal representative, or assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(iii). Status of Claims:

Claims 36-58 are pending.

No claims stand withdrawn.

Claims 36-58 stand rejected.

The rejection of claims 36-58 is appealed.

Please see the Claims Appendix for a copy of the claims under appeal.

(iv). Status of any Amendment Filed Subsequent to Final Rejection:

No amendment was filed subsequent to the Final Office Action mailed 3 August 2010. A Notice of Appeal was timely filed on 2 February 2011 along with a petition for extension of time.

(v). Summary of Claimed Subject Matter:

Independent claim 36 provides a process for preparing a stable granulate for reconstitution with water into an oral aqueous suspension comprising micronized amoxicillin trihydrate and sugar, the process comprising:

screening a mixture of amoxicillin trihydrate and sugar through a first sieve to provide a sieved mixture;

extruding the sieved mixture with a granulation liquid comprising water to obtain a wet extruded mass;

screening the wet extruded mass through a second sieve to provide a sieved wet extruded mass;

drying the sieved wet extruded mass to form a dried sieved extruded mass; and

homogenizing the dried sieved extruded mass to obtain a granulate comprising micronized particles of amoxicillin, wherein the granulate is dissolvable in water to form a smooth suspension. Basis for claim 36 can be found in the originally filed application including at pages 6-7.

Independent claim 55 provides process for preparing a stable granulate for reconstitution with water into an oral aqueous suspension comprising micronized amoxicillin trihydrate and sugar, the process comprising:

screening a mixture of amoxicillin trihydrate and sugar through a first sieve to provide a sieved mixture;

extruding the sieved mixture with a granulation liquid comprising water to obtain a wet extruded mass;

screening the wet extruded mass through a second sieve to provide a sieved wet extruded mass;

drying the sieved wet extruded mass to form a dried sieved extruded mass; and

homogenizing the dried sieved extruded mass to obtain a granulate comprising micronized particles of amoxicillin, the particles of amoxicillin having a size range of

between 0.1 µm to 100 µm, wherein the granulate is dissolvable in water to form a smooth suspension. Basis for claim 36 can be found in the originally filed application including at pages 6-7.

Independent claim 58 provides a process for preparing a stable granulate for reconstitution with water into an oral aqueous suspension comprising micronized amoxicillin trihydrate and sugar, the process comprising forming the granulate by compacting a mixture of amoxicillin trihydrate, sugar and water. Basis for claim 36 can be found in the originally filed application including at pages 6-7.

(vi). Grounds of Rejection to be Reviewed on Appeal:

A. Whether claim 47 complies with 35 U.S.C. 112, first paragraph.

B. Whether claims 48 and 49 comply with 35 U.S.C. 112, first paragraph.

C. Whether claims 36, 38, 39, 41-46, 50, 53, 54 and 58 are anticipated under 35 U.S.C. 102(b) over EP 0 080 862 (Grimmett).

D. Whether claim 51 is anticipated under 35 U.S.C. 102(b) over Grimmett as evidenced by U.S. Patent No. 7,157,094 (Gaytan).

E. Whether claim 37 is patentable under 35 U.S.C. 103(a) over Grimmett in view of U.S. Patent No. 6,242,382 (Bratz) further in view of U.S. Patent No. 4,177,254 (Khan).

F. Whether claims 40 and 52 are patentable under 35 U.S.C. 103(a) over Grimmett in view of U.S. published patent application No. 2002/0006433 (Davidson).

G. Whether claims 55-57 are patentable under 35 U.S.C. 103(a) over Grimmett in view of published international patent application No. WO 03/063820 (Schwartz).

(vii). Argument:

A. Claim 47 complies with 35 U.S.C. 112, first paragraph.

The originally filed specification at page 5, second paragraph, discloses that "the loss of crystallization water of amoxicillin trihydrate caused by applied pressure and temperature between 30° to 100°C is compensated for by the addition of water." One of ordinary skill in the art is well aware of how to measure the "loss of crystallization water" without undue experimentation. This disclosure supports claim 47, which recites "the water in the granulation liquid is added in an amount to compensate for the loss of crystallization water of the amoxicillin trihydrate caused by extrusion."

The Examiner argues that "the specification does not disclose the actual concentration of water in the granulation liquid that is required to compensate for the loss of crystallization water of the amoxicillin trihydrate caused by extrusion." Since one of ordinary skill in the art can readily determine the required amount water without undue experimentation, no disclosure on the amount of water is required. Furthermore, one of ordinary skill in the art is well aware that the amount of crystallization water lost will depend on the amount of amoxicillin trihydrate being extruded and, thus, no specific amount of such water can be provided in the specification.

Appellant respectfully submits that the process recited in claim 47 fully complies with Section 112 and withdrawal of the rejection is respectfully requested.

B. Claims 48 and 49 comply with 35 U.S.C. 112, first paragraph.

Claims 48 and 49 do not stand or fall together.

Claim 48 recites that "the granulate is free of pharmaceutically acceptable excipients." Claim 48 is supported by the originally filed specification at page 5, first paragraph and page 7, second paragraph, which discloses that the extrusion process is preferably conducted without the addition of "pharmaceutically acceptable excipients" so

that they are omitted from the obtained granulate. The originally filed specification distinguishes between the required "sugar" and "pharmaceutically acceptable excipients." Sugar is not listed in the examples of "pharmaceutically acceptable excipients" disclosed in paragraph 5, first paragraph. Reading and comprehending the specification, one of ordinary skill in the art will not be confused by sugar being a required ingredient in the claimed process, and excipients being excluded.

Appellant respectfully submits that the process recited in claim 48 fully complies with Section 112 and withdrawal of the rejection is respectfully requested.

Claim 49 recites that "the granulate is free of thickeners, lubricants, disintegrants, preservatives, dessicants, stabilizing agents, flavoring agents, dyes, and suspension agents." The originally filed specification at page 5, first paragraph, provides support for omitting "thickeners, lubricants, disintegrants, preservatives, dessicants, stabilizing agents, flavoring agents, dyes, and suspension agents" from the granulate.

The originally filed specification distinguishes sugar, which is a sweetener, from "flavoring agents." See page 3, third paragraph, line 9, which lists "sweetening agents" separate from "flavoring agents." Furthermore, the supporting description at page 5, first paragraph in the specification only omits "flavoring agents," and does not omit "sweetening agents." Reading and comprehending the specification, one of ordinary skill in the art will not be confused by sugar being a required ingredient in the claimed process, and flavoring agents being excluded.

Appellant respectfully submits that the process recited in claim 49 fully complies with Section 112 and withdrawal of the rejection is respectfully requested.

C. Claims 36, 38, 39, 41-46, 50, 53, 54 and 58 are not anticipated under 35 U.S.C. 102(b) over EP 0 080 862 (Grimmett).

Claims 36, 38, 39, 41-46, 50, 53, and 54 stand or fall together for purpose of this appealed Section 102(b) rejection only.

Claim 58 does not stand or fall with any other claim.

The rejection of claims 36, 38, 39, 41-46, 50, 53, 54 and 58 under 35 U.S.C. § 102(b) as being anticipated by EP 0 080 862 (Grimmett) is respectfully traversed. The claimed invention is not anticipated by Grimmett for the following reasons.

Claims 36-57 recite "extruding the sieved mixture with a granulation liquid comprising water to obtain a wet extruded mass." Claim 58 recites compacting a mixture comprising "water."

Grimmett excludes the addition of water during the extruding step (also referred to as compacting). See page 1, last line of Grimmett, which states that "a non-hygroscopic water soluble binder" should be used. Grimmett, at page 2, lines 8 to 12, further discloses that the employed materials should have low free moisture content, should be pre-dried, and "advantageously an edible desiccant may be incorporated in the composition." A desiccant is a "drying agent," which is the opposite of adding water. Grimmett at page 2 then goes on to provide a list of suitable solvents for use when forming the extrudate and among the many standard solvents mentioned (methanol, ethanol, acetone, methyl acetate, etc.) water is not included. Grimmett further teaches on page 3, lines 7 to 10, that the formulation process should be carried out under a dry atmosphere. The only time Grimmett teaches to use water is after extrusion and formation of the dry particles, i.e. the dry particles are suspended in water to form a solution that is consumed by a patient. See page 3, lines 15-23 of Grimmett. Based on these teachings in Grimmett, one of ordinary skill in the art would understand that no water should be added during the extrusion process.

In contrast, the claimed invention requires the addition of water so that a wet mass containing water is produced during the extrusion step. Examples 2 and 3 in the originally filed application disclose exemplary amounts of water being added to the composition before extrusion.

Example 4 of Grimmett prepared a water-free, wet mass containing dichloromethane as the solvent. Prior to the present invention it was believed that water destabilized the granulate. Page 2, lines 13-14 of Grimmett teaches that "tightly bound

water, such as water of crystallization normally has little adverse effect on stability," which clearly infers that added water would have an adverse effect on stability.

In response to the above arguments, the Examiner argues that:

> Applicant's main argument is that the granulation liquids disclosed by Grimmett do not contain water. However, as explained in the 35 USC 102(b) rejection, above, newly presented claim 36 claims a "granulation liquid comprising water." This limitation does not include a lower limit water concentration: as such, one molecule of water in the granulation liquid reads on claims 36 and 58 as currently constructed. Grimmett teaches that formulation of the disclosed composition can take place in an atmosphere of up to 40% relative humidity (see page 3, line 9). In an atmosphere of up to 40% relative humidity, hygroscopic hydrophilic organic solvents such as methanol, ethanol, n- and iso-propanol will inherently contain at least one molecule of water, reading on claim 36 as currently constructed.

Appellant respectfully submits that claim 36 does not merely recite a "granulation liquid comprising water." Claim 36 specifically recites "extruding the sieved mixture with a granulation liquid comprising water to obtain a wet extruded mass," which clearly requires the active process step of adding far more than a single molecule of water to form the wet extruded mass.

In contrast, as discussed above, Grimmett teaches away from adding water to the extrusion process by teaching that unbound water causes instability and by teaching to use dry ingredients, a desiccant, non-hygroscopic ingredients, organic solvents, and perform the extrusion in a dry atmosphere.

In view of the differences between Grimmett and the claimed invention, withdrawal of the Section 102 rejection is respectfully requested.

Claim 58 is separately patentable.

Claim 58 recites "forming the granulate by compacting a mixture of amoxicillin trihydrate, sugar and water." As discussed above, Grimmett specifically teaches to avoid adding water during the extrusion (compaction) by teaching that unbound water

causes instability and by teaching to use dry ingredients, a desiccant, non-hygroscopic ingredients, organic solvents and perform the extrusion in a dry atmosphere. In view of the differences between Grimmett and claim 58, withdrawal of the Section 102 rejection is respectfully requested.

D. Claim 51 is not anticipated under 35 U.S.C. 102(b) over EP 0 080 862 (Grimmett) as evidenced by U.S. Patent No. 7,157,094 (Gaytan).

Grimmett has been distinguished from claim 36 for the reasons provided above. Claim 51 depends upon claim 36 and , thus, includes the limitations of claim 36. In view of the differences between Grimmett and claim 51, withdrawal of the Section 102 rejection is respectfully requested.

E. Claim 37 is patentable under 35 U.S.C. 103(a) over Grimmett in view of U.S. Patent Nos 6,242,382 (Bratz) further in view of U.S. Patent No. 4,177,254 (Khan).

Claim 37 recites that "the granulation liquid further comprises sugar." Thus, the granulation liquid comprises at least sugar and water. Claim 37 depends from claim 36 and, thus, includes all of the limitations of claim 36. Claim 36 has been distinguished from Grimmett for the many reasons provided above. Bratz and Khan do not provide the deficiencies of Grimmett for the following reasons.

Bratz discloses a solid mixture of sulfonylurea and an adjuvant for use in killing undesirable harmful plants to protect crops. See column 1, lines 7-9 and column 2, lines 4-38. The solid compositions are dispersed in a liquid and applied to the crop field. Among the many different methods of making the solid composition, extrusion is disclosed at column 14, lines 13-33. Among the many suitable components, aqueous sugars are listed as suitable granulation liquids. However, one of ordinary skill in the art would not be motivated to use Bratz's aqueous sugar as a granulation liquid in the process of Grimmett for at least the following two reasons.

(1) Bratz's teaches an extrusion method to form a pesticide that is not consumable, and Grimmett relates to a method of making an antibiotic that is consumable.

(2) As discussed above, Grimmett specifically teaches to avoid adding water to the extrusion process because it causes instability. Grimmett also teaches against adding water by teaching to use dry ingredients, a desiccant, non-hygroscopic ingredients, organic solvents and perform the extrusion in a dry atmosphere.

One of ordinary skill in the art would not ignore these teachings in Grimmett to avoid water and add water to the extrusion process.

Kahn discloses forming a coating layer of amoxicillin trihydrate and sucrose on a sucrose core. See column 1, lines 38-42. The sucrose is used as binder for the amoxicillin trihydrate coating. See column 2, lines 48-57. However, Kahn does not disclose that sucrose liquid should be used as a granulation liquid in an extrusion process.

Appellant respectfully submits that the Examiner has not provided a prima facie case of obviousness, since one of ordinary skill in the art would not use a water/sugar solution (Bratz and Kahn) in the process of Grimmett that teaches to avoid adding water to the extrusion process. For this reason alone, the Section 103 rejection should be withdrawn.

The unexpected advantages of record rebut any prima facie case of obviousness raised by the Examiner. A major problem associated with conventional amoxicillin granules is that they agglomerate and do not form a smooth suspension upon reconstitution, and excipients, such as lubricants, thickeners, suspension agents, etc. are required.

The present invention provides a process for the production of a stable amoxicillin granulate that is more adapted for the use in paediatric and geriatric patients, which does not require the use of excipients and provides a smooth suspension upon reconstitution. Such a product providing a smooth suspension on reconstitution

improves the compliance of patients in taking a medicament, especially if the medicament is taken in larger amounts as is often required in the field of antibiotics.

The present invention provides a water-based extrusion process followed by sieving, drying and homogenization steps. This process generates small-size amoxicillin particles while at the same time avoiding formation of agglomerates and the produced granulate forms a smooth suspension upon reconstitution with water, as can be seen from Fig. 1 in the present specification. See page 9, 2nd and 3rd paragraphs of the originally filed application. Sample D represents the claimed invention, which surprisingly showed no formation of amoxicillin agglomerates during suspension. In contrast, Sample A represents prior art "wet granulation techniques" (without the water/sugar granulation liquid) in which agglomerates of the amoxicillin granules occurred. Sample A represents the water-free, wet process of Grimmett in which no water was added in the granulation liquid. See Example 4 of Grimmett in which dichloromethane was used in a water-free wet process.

The effect of large size particles on oral texture and palatability in suspensions is an issue which has been addressed in various examinations, e. g. Tyle, "Effect of size, shape and hardness of particles in suspension on oral texture and palatability," Acta Psychologica 84 (1993) pp. 111-118, copy filed on 24 May 2010. Tyle teaches that the characteristics of particles in suspension can cause a problem in drug development due to a lack of compliance of patients if the particles in suspension are too large. If the suspension contains a considerable amount of agglomerates or big sized particles the suspension effects a gritty, very unpleasant taste on ingestion. See page 118, last paragraph of Tyle. Tyle does not teach or suggest how to make particles free of agglomerates or big sized particles. The claimed process provides a granulate that lacks large-sized amoxicillin particles and/or agglomerates, thus, solving the problem of preventing grittiness on the sensitive human tongue upon ingestion.

Appellant also found that the addition of water to the extrusion process, along with sugar, surprisingly did not destabilize the granulate. See page 9, first and second paragraphs in the present specification. In contrast, Grimmett teaches that "tightly

bound water, such as water of crystallization, normally has little adverse effect on stability," which clearly infers that added water has an adverse effect on stability. See page 2, lines 13-14 of Grimmett.

In view of the differences between the claimed invention and the theoretical combination of references, and the unexpected advantages of the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

F. Claims 40 and 52 are patentable under 35 U.S.C. 103(a) over Grimmett in view of U.S. published patent application No. 2002/0006433 (Davidson).

Claims 40 and 52 stand or fall stand or fall together for purpose of this appealed Section 103(a) rejection only.

The rejection of claims 40 and 52 under 35 U.S.C. 103(a) as being unpatentable over Grimmett in view of U.S. Published Patent Application No. 2002/0006433 (Davidson) is respectfully traversed. The claimed invention is not taught or suggested by the theoretical combination of references for the following reasons.

Claims 40 and 50 depend upon claim 36 and, thus, include the limitations of claim 36. Claim 36 has been distinguished form Grimmett for the reasons provided above and Davidson does not provide the deficiencies of Grimmett.

As discussed above, Grimmett specifically teaches to avoid adding water to the extrusion method because it causes instability. Grimmett also teaches against adding water by teaching to use dry ingredients, a desiccant, non-hygroscopic ingredients, organic solvents, and to perform the extrusion in a dry atmosphere. One of ordinary skill in the art would not ignore these teachings in Grimmett to avoid adding water to the extrusion process.

Davidson also does not teach or suggest adding water to a mixture of amoxicillin trihydrate and sugar so that a wet mass is extruded during an extruding step. Thus, the combination of Grimmett and Davidson teaches to avoid adding water during the extrusion step, which is in a direction away from the claimed invention. For this reason,

the Examiner has not provided a prima facie case of obviousness and the Section 103 rejection should be withdrawn.

The unexpected advantages of record rebut any prima facie case of obviousness. A major problem associated with conventional amoxicillin granules is that they agglomerate and do not form a smooth suspension upon reconstitution, and excipients, such as lubricants, thickeners, suspension agents, etc. are required.

The present invention provides a process for the production of a stable amoxicillin granulate that is more adapted for the use in paediatric and geriatric patients, which does not require the use of excipients and provides a smooth suspension upon reconstitution. Such a product providing a smooth suspension on reconstitution improves the compliance of patients in taking a medicament, especially if the medicament is taken in larger amounts as is often required in the field of antibiotics.

The present invention provides a water-based extrusion process followed by sieving, drying and homogenization steps. This process generates small-size amoxicillin particles while at the same time avoiding formation of agglomerates and the produced granulate forms a smooth suspension upon reconstitution with water, as can be seen from Fig. 1 in the present specification. See page 9, 2nd and 3rd paragraphs of the originally filed application. Sample D represents the claimed invention, which surprisingly showed no formation of amoxicillin agglomerates during suspension. In contrast, Sample A represents prior art "wet granulation techniques" (without the water/sugar granulation liquid) in which agglomerates of the amoxicillin granules occurred. Sample A represents the water-free, wet process of Grimmett in which no water was added in the granulation liquid. See Example 4 of Grimmett in which dichloromethane was used in a water-free, wet process.

The effect of large size particles on oral texture and palatability in suspensions is an issue which has been addressed in various examinations, e. g. Tyle, "Effect of size, shape and hardness of particles in suspension on oral texture and palatability," Acta Psychologica 84 (1993) pp. 111-118, copy filed on 24 May 2010. Tyle teaches that the characteristics of particles in suspension can cause a problem in drug development due

to a lack of compliance of patients if the particles in suspension are too large. If the suspension contains a considerable amount of agglomerates or big sized particles the suspension effects a gritty, very unpleasant taste on ingestion. See page 118, last paragraph of Tyle. Tyle does not teach or suggest how to make particles free of agglomerates or big sized particles. The claimed process provides a granulate that lacks large-sized amoxicillin particles and/or agglomerates, thus, solving the problem of preventing grittiness on the sensitive human tongue upon ingestion.

Appellant also found that the addition of water to the extrusion process, along with sugar, surprisingly did not destabilize the granulate. See page 9, first and second paragraphs in the present specification. In contrast, Grimmett teaches that "tightly bound water, such as water of crystallization, normally has little adverse effect on stability," which clearly infers that added water has an adverse effect on stability. See page 2, lines 13-14 of Grimmett.

In view of the differences between the claimed invention and the theoretical combination of references, and the advantages of the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

G. Claims 55-57 are patentable under 35 U.S.C. 103(a) over Grimmett in view of published international patent application No. WO 03/063820 (Schwartz).

Claims 55-57 stand or fall stand or fall together for purpose of this appealed Section 103(a) rejection only.

The rejection of claims 55-57 under 35 U.S.C. 103(a) as being unpatentable over Grimmett in view of Schwartz is respectfully traversed. The claimed invention is not taught or suggested by the theoretical combination of references for the following reasons.

Claims 55-57 require the following steps:

screening a mixture of amoxicillin trihydrate and sugar through a first sieve to provide a sieved mixture;

extruding the sieved mixture with a granulation liquid comprising water to obtain a wet extruded mass;

screening the wet extruded mass through a second sieve to provide a sieved wet extruded mass;

drying the sieved wet extruded mass to form a dried sieved extruded mass; and

homogenizing the dried sieved extruded mass to obtain a granulate comprising micronized particles of amoxicillin, the particles of amoxicillin having a size range of between 0.1 µm to 100 µm, wherein the granulate is dissolvable in water to form a smooth suspension.

Appellant respectfully submits that the Examiner has not provided a prima face case of obviousness. As discussed above, Grimmett specifically teaches to avoid adding water to the extrusion process because it causes instability. Grimmett also teaches to avoid adding water by teaching to use dry ingredients, a desiccant, non-hygroscopic ingredients, organic solvents, and to perform the extrusion in a dry atmosphere. One of ordinary skill in the art would not ignore these teachings in Grimmett to avoid adding water to the extrusion process. For this reason alone, the Section 103 rejection should be withdrawn.

Schwartz discloses granulation of a beta-lactam antibiotic and a beta-lactamase inhibitor. Schwartz teaches using granulation liquids that may or may not contain water. Page 5, lines 14-19. While Schwartz teaches that the composition may optionally contain an excipient, Schwartz teaches that when moist-granulating preferably no excipient is added during the whole process See page 6, lines 24-26. A long list of excipients are disclosed at page 12, lines 5-13, of which sugar is listed. Note that while sugar is included as an "excipient" in Schwartz, the present specification distinguishes sugar from excipients as discussed above. Thus, Schwartz teaches against using sugar when the granulation is conducted under moist conditions, such as wet extrusion.

The unexpected results of record rebut any prima facie case of obviousness. A major problem associated with conventional amoxicillin granules is that they agglomerate and do not form a smooth suspension upon reconstitution, and excipients,

such as lubricants, thickeners, suspension agents, etc. are required.

The present invention provides a process for the production of a stable amoxicillin granulate that is more adapted for the use in paediatric and geriatric patients, which does not require the use of excipients and provides a smooth suspension upon reconstitution. Such a product providing a smooth suspension on reconstitution clearly improves the compliance of patients in taking a medicament, especially if the medicament is taken in larger amounts as is often required in the field of antibiotics.

The present invention provides a water-based extrusion process followed by sieving, drying and homogenization steps. This process generates small-size amoxicillin particles while at the same time avoiding formation of agglomerates and the so produced granulate forms a smooth suspension upon reconstitution with water, as can be seen from Fig. 1 in the present specification. See page 9, 2nd and 3rd paragraphs of the originally filed application. Sample D represents the claimed invention, which surprisingly showed no formation of amoxicillin agglomerates during suspension. In contrast, Sample A represents prior art "wet granulation techniques" (without the water/sugar granulation liquid) in which agglomerates of the amoxicillin granules occurred. Sample A represents the wet process of Grimmett in which no water was added in the granulation liquid. See Example 4 of Grimmett in which dichloromethane was used in a water-free, wet process. Sample A also represents the wet processes disclosed in Schwartz which do not use water as the liquid.

The effect of large size particles on oral texture and palatability in suspensions is an issue which has been addressed in various examinations, e. g. Tyle, "Effect of size, shape and hardness of particles in suspension on oral texture and palatability," Acta Psychologica 84 (1993) pp. 111-118, copy filed on 24 May 2010. Tyle teaches that the characteristics of particles in suspension can cause a problem in drug development due to a lack of compliance of patients if the particles in suspension are too large. If the suspension contains a considerable amount of agglomerates or big sized particles the suspension effects a gritty, very unpleasant taste on ingestion. See page 118, last

paragraph of Tyle. Tyle does not teach or suggest how to make particles free of agglomerates or big sized particles.

Appellant also found that the addition of water to the extrusion process, along with sugar, surprisingly did not destabilize the granulate. See page 9, first and second paragraphs in the present specification. In contrast, Grimmett teaches that "tightly bound water, such as water of crystallization, normally has little adverse effect on stability," which clearly infers that added water has an adverse effect on stability. See page 2, lines 13-14 of Grimmett.

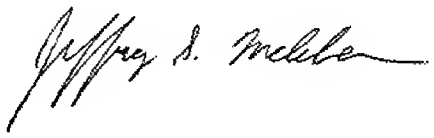
The novel wet extrusion process of the present invention surprisingly provides a granulate wherein the particles of amoxicillin contained therein are of a specific small particle size and are free of agglomeration. This granulate has the ability to decompose to fine particles of micronized amoxicillin trihydrate, which results in a smooth suspension on reconstitution with water. The size of micronized amoxicillin trihydrate particles in the aqueous suspension obtained after reconstitution exhibits a small range of less than 100 µm, with the majority of particles being within the range of 1 to 30 µm. See page 9, second paragraph of the present specification. The granulate of the present invention, which lacks large-sized amoxicillin particles and/or agglomerates, thus, solves the problem of preventing grittiness on the sensitive human tongue upon ingestion.

In view of the differences between the claimed invention and the theoretical combination of references, and the advantages of the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

Conclusion

In view of the lack of *prima facie* cases of anticipation and obviousness, the many differences between the claimed invention and the cited references, and the unexpected advantages of the claimed invention, it is believed that this application clearly and patentably distinguishes over the combination of the cited references and is in proper condition for allowance. Accordingly, Appellant respectfully request that the Board allow claims 36-58 over the cited references.

Respectfully submitted,
Manelli Denison & Selter, PLLC



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(viii) Claims Appendix:

Claims 1-35 (Cancelled)

36. (Previously Presented) A process for preparing a stable granulate for reconstitution with water into an oral aqueous suspension comprising micronized amoxicillin trihydrate and sugar, the process comprising:

screening a mixture of amoxicillin trihydrate and sugar through a first sieve to provide a sieved mixture;

extruding the sieved mixture with a granulation liquid comprising water to obtain a wet extruded mass;

screening the wet extruded mass through a second sieve to provide a sieved wet extruded mass;

drying the sieved wet extruded mass to form a dried sieved extruded mass; and

homogenizing the dried sieved extruded mass to obtain a granulate comprising micronized particles of amoxicillin, wherein the granulate is dissolvable in water to form a smooth suspension.

37. (Previously Presented) The process according to claim 36, wherein the granulation liquid further comprises sugar.

38. (Previously Presented) The process according to claim 36, wherein the sugar is selected from the group consisting of sucrose, lactose, sugar alcohols and maltodextrins alone or in combination.

39. (Previously Presented) The process according to claim 36, wherein the sugar comprises sucrose.

40. (Previously Presented) The process according to claim 36, wherein the sugar comprises mannitol or sorbitol.

41. (Previously Presented) The process according to claim 36, wherein the micronized amoxicillin trihydrate is present in an amount of from 1 to 80% by weight of the granulate.

42. (Previously Presented) The process according to claim 36, wherein the micronized amoxicillin trihydrate is present in an amount of from 5 to 50% by weight of the granulate.

43. (Previously Presented) The process according to claim 36, wherein the micronized amoxicillin trihydrate is present in an amount of from 10 to 30% by weight of the granulate.

44. (Previously Presented) The process according to claim 36, wherein the sugar comprises sucrose, and the sucrose is present in an amount of from 20 to 99% by weight of the granulate.

45. (Previously Presented) The process according to claim 36, wherein the particle size of the granulate is in the range of from 200 to 3000 µm.

46. (Previously Presented) The process according to claim 36, wherein the particle size of the granulate is in the range of from 500 to 1500 µm.

47. (Previously Presented) The process according to claim 36, wherein the water in the granulation liquid is added in an amount to compensate for the loss of crystallization water of the amoxicillin trihydrate caused by extrusion.

48. (Previously Presented) The process according to claim 36, wherein the granulate is free of pharmaceutically acceptable excipients.

49. (Previously Presented) The process according to claim 36, wherein the granulate is free of thickeners, lubricants, disintegrants, preservatives, dessicants, stabilizing agents, flavoring agents, dyes, and suspension agents.

50. (Previously Presented) The process according to claim 36, wherein the process is conducted without the use of grinding or micronizing the mixture of amoxicillin trihydrate and sugar.

51. (Previously Presented) The process according to claim 36, wherein the extrusion is conducted at a temperature between 30°C to 100°C.

52. (Previously Presented) The process according to claim 36, wherein the homogenization is conducted in a tumbler mixer.

53. (Previously Presented) The process according to claim 36, wherein the first and second sieves have a mesh size between 0.5 mm to 4.0 mm.

54. (Previously Presented) The process according to claim 36, wherein the first and second sieves have a mesh size of 1 mm to 2 mm.

55. (Previously Presented) A process for preparing a stable granulate for reconstitution with water into an oral aqueous suspension comprising micronized amoxicillin trihydrate and sugar, the process comprising:

screening a mixture of amoxicillin trihydrate and sugar through a first sieve to provide a sieved mixture;

extruding the sieved mixture with a granulation liquid comprising water to obtain a wet extruded mass;

screening the wet extruded mass through a second sieve to provide a sieved wet extruded mass;

drying the sieved wet extruded mass to form a dried sieved extruded mass; and

homogenizing the dried sieved extruded mass to obtain a granulate comprising micronized particles of amoxicillin, the particles of amoxicillin having a size range of between 0.1 µm to 100 µm, wherein the granulate is dissolvable in water to form a smooth suspension.

56. (Previously Presented) The process according to claim 55, wherein the particles of amoxicillin having a size range of between 0.5 µm to 50 µm.

57. (Previously Presented) The process according to claim 55, wherein major particles of amoxicillin having a size within a range of from 1 µm to 30 µm.

58. (Previously Presented) A process for preparing a stable granulate for reconstitution with water into an oral aqueous suspension comprising micronized amoxicillin trihydrate and sugar, the process comprising forming the granulate by compacting a mixture of amoxicillin trihydrate, sugar and water.

(ix) Evidence Appendix:

Tyle, "Effect of size, shape and hardness of particles in suspension on oral texture and palatability," Acta Psychologica 84 (1993) pp. 111-118, copy filed on 24 May 2010.

(x) Related Proceedings Appendix:

Not applicable.